

IN FOCUS

Next Directions in the Neuroscience of Cancers Arising outside the CNS



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Summary: The field of cancer neuroscience has begun to define the contributions of nerves to cancer initiation and progression; here, we highlight the future directions of basic and translational cancer neuroscience for malignancies arising outside of the central nervous system.

INTRODUCTION

Fundamental work centered on the (epi)genetic and cellular mechanisms of oncogenesis revealed that these changes are necessary but insufficient for explaining all aspects of cancer. Complementary research demonstrated that tumor cells reciprocally interact with numerous non-neoplastic cell types in their surrounding milieu to dictate cancer initiation, growth, progression, and response to therapies (1). The recognition of the importance of these cells within the tumor microenvironment (TME) has heralded a significant paradigm shift in oncology, perhaps best exemplified by key advancements in cancer angiogenesis and immunotherapy. The nervous system, comprised of central (brain, spinal cord, and retina) and peripheral (autonomic, sensory, enteric, and motor) components, has also emerged as a major cancer driver. However, neurons are one of the cell types often overlooked in the TME, partly because their cell bodies reside outside of the primary tumor (within ganglia

or central nuclei). Until recently, we have not had the technical ability to label and phenotype small nerve endings within the TME at high resolution (e.g., via spatial transcriptomics, multiplex immunofluorescence). Additionally, cancer scientists have been primarily focused on major discoveries in genetics, tumor angiogenesis, and anti-tumor immunity, while neuroscientists have been transfixed on understanding neurodegenerative diseases and cognitive impairments, leaving tumor–nerve interactions largely unexplored. In this perspective, we assembled a team of experts in cancer neuroscience to discuss the potential roles of the nervous system in cancer development and progression outside of the central nervous system and provide an outline of future directions for research investigation.

REGULATION OF CANCER BY LOCAL NERVES

Analogous to tumor angiogenesis, in which cancer cells release factors that elicit the growth of blood vessels into

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the tumor, cancer cell interactions with nerves induce a neurodevelopmental response that promotes axonogenesis (i.e., neurite outgrowth) into the TME (2). These tumor-associated nerves are different from the pre-existing normal neuronal network and carry novel functions that can be targeted to mitigate tumor development and progression. Over the past several years, fundamental discoveries have positioned the autonomic nervous system, comprised of sympathetic and parasympathetic components, as a major player in cancer development and progression.

Sympathetic and parasympathetic nerves release norepinephrine (aka noradrenaline) and acetylcholine as their primary neurotransmitters, respectively. Sympathetic nerves play a vital role in triggering the “fight or flight” response and mediate involuntary stress-related biological processes, while parasympathetic nerves help reestablish homeostasis and mediate physiologic functions during rest. Although the physiologic effects of these neural signals are well-defined, their relative contributions to tumorigenesis and cancer progression are yet to be fully explored. Frequently, they seem to provide complementary physiologic functions, with sympathetic signaling often enhancing the first stages of tumor development and parasympathetic signaling controlling tumor progression (3). However, their specific effects usually differ across tumor sites (e.g., breast, prostate, gastric, pancreas), and have differential influences on tumor cells and stromal components within the TME. Sympathetic innervation seems to regulate tumor vasculature and induce immune suppression but can also act directly on cancer cells to promote disease progression. So far, our understanding of parasympathetic contributions to components of the TME is incompletely defined, but existing work suggests differential effects are likely due to site-specific receptor expression and innervation patterns. This sympathetic/parasympathetic balance will need to be considered while contemplating clinical trials using new or repurposed drugs to target these autonomic neuronal signals (e.g., beta-blockers). Developing novel tools (e.g., viral vectors) to monitor and manipulate select populations of tumor-associated nerves will allow for site- and neuron-specific mapping and tracing within solid tumors (3). In addition, using viral vectors to map and manipulate metastasis-associated nerves represents a major research opportunity moving forward.

In addition to autonomic innervation, many types of tumors also contain sensory nerves, including nociceptors. These nociceptor neurons not only contribute to cancer-associated pain but also promote cancer progression through the release of neuropeptides (e.g., calcitonin gene-related peptide; CGRP). Our current knowledge of these interactions is limited; however, cross-talk between the sensory and immune systems is becoming clearer. By using therapeutic approaches that silence nociceptor neurons in combination with conventional immunotherapies, such interactions may be exploited to reverse dysfunctional immune responses and achieve durable antitumor immunity (4). Such an approach at the intersection of neuroscience, immunology, and oncology should be investigated further in other cancer contexts. In addition, studies on sensory nerves within tumors can provide valuable information on how pain signals are relayed to the brain, and how the brain subsequently sends signals back down to the tumor to promote its development and growth (5).

Future studies should aim to understand local bidirectional interactions between sensory neurons (including nociceptors) and cancer cells, focusing on how cancer cells may alter neuronal characteristics, functionality, and excitability. Given the highly heterogeneous nature of tissue innervation, coupled with the diverse immune landscape of peripheral organs, it is likely that sensory neurons regulate site-specific anti-tumor immunity in multiple different ways. An additional layer of complexity involves local interplay among different types of nerve fibers, including sensory, adrenergic, and cholinergic nerves within a tumor. This interneural cross-talk could also be instructive in shaping the local tumor-immune microenvironment. A comprehensive approach combining retrograde nerve tracing, spatially resolved transcriptomics, and high-dimensional immune profiling together will be essential.

“TOP-DOWN” CONTROL OF CANCER DEVELOPMENT

A unique aspect of the peripheral nervous system is that it is directly controlled by “top-down” signals originating in the brain and spinal cord. In this manner, changes in the activity of specific brain neuronal populations can have downstream effects on peripheral tissues within the body. This is well illustrated by the subjective experience of stress, which activates many brain regions (including the paraventricular nucleus of the hypothalamus; PVN) to drive output from the autonomic nervous and neuroendocrine systems. These, in turn, elicit diverse “system-wide” effects, including elevations in heart rate, release of hormones (e.g., cortisol), and immune alterations throughout the body. Recent studies demonstrate that this “top-down” signaling can also regulate cancer progression (5–7).

Tracing studies have expanded our understanding of the extent of the connection between tumor-infiltrating nerves embedded in the tumor bed and the brain. For example, neurons in the amygdala that modulate anxiety-related behaviors become aberrantly active during primary breast cancer progression (7). Using polysynaptic tracing techniques (i.e., pseudorabies virus), it has been shown that newly formed sympathetic neurites within the TME develop long-range connections to the brain. These neurons trigger sympathetic output to the primary breast tumor, increasing local norepinephrine release and enhancing tumor growth. This promotes marked changes in the intratumor immune landscape that could be rescued by pharmacologic treatment with the anxiolytic benzodiazepine alprazolam. In a separate but similar study, researchers identified a ventrolateral medullary circuit in the brainstem that promotes colon adenocarcinoma tumor progression via sympathetic nerve-mediated immunomodulation (6). Additional work demonstrated that neural progenitors from the subventricular zone, a neurogenic area in the brain, can distally influence prostate cancer neo-neurogenesis to influence disease progression (8).

Studies such as these highlight the complex interplay between neuronal networks in the brain, downstream autonomic nerve activity, and tumor development. Building on work in the CNS, using state-of-the-art neuroscience tools (e.g., viral tract tracing, optogenetics/chemogenetics) in the context of cancers outside the brain provides unique opportunities to evaluate the role of specific neural circuits and cell

types in dictating cancer initiation, development, progression, spread, and therapeutic resistance.

NEUROTOXIC EFFECTS OF CANCER THERAPIES

The nervous system often receives “collateral” damage throughout cancer therapy. One aspect of such neurotoxicity is chemotherapy-induced peripheral neuropathy (CIPN), characterized by a “dying back” of sensory axons innervating the extremities (i.e., hands and feet) that results in numbness and pain. This process begins at nerve terminals and progresses retrogradely, is widespread following treatment with diverse antineoplastic agents, and is especially common (>60%) in response to platinum-based drugs, taxanes, thalidomide, and ixabepilone, among others (9). Mechanistically, some aspects of CIPN pathophysiology are becoming clear. Taxanes (e.g., paclitaxel) can act directly on sensory axons to promote their degeneration by reducing the expression of Bcl-w. This pro-survival protein signal normally functions through binding IP₃R1 in neurons to prevent axonal degeneration (10). Methods of mitigating CIPN are currently restricted to dose limitation or early termination of chemotherapy, which undermines therapeutic responses and patient survival. Much remains to be learned about the mechanisms that underpin CIPN and how to therapeutically address this widespread problem that results in chronic neuropathic pain for millions of cancer survivors. More work will be required to understand how anticancer therapies influence the peripheral nervous system, whether this creates a harmful feedback loop with the promotion of tumor progression, and how these interactions dictate therapeutic efficacy. Clinically, a better assessment of “systemic” versus tumor-intrinsic peripheral neuropathy is needed to guide preclinical work. A multidisciplinary, “team science” approach involving neuroscientists, immunologists, medicinal chemists, and cancer biologists is needed to better understand and effectively treat CIPN and other forms of chemotherapy-induced neurotoxicity.

OUTSTANDING QUESTIONS

Substantial work remains to refine and extend our understanding of nerve–cancer interactions. Pioneering studies have revealed that (a) tumors can excite and remodel local and long-range nerves, (b) nerves within tumors can modulate antitumor immunity and angiogenesis, and (c) brain activity can influence distal tumors via the autonomic nervous system. Several research areas must be integrated into our scientific thinking in order to advance this new field (Fig. 1).

The first is to examine electrochemical (or synaptic) communication between peripheral nerves and tumor cells, an emerging hallmark of brain cancers and tumors metastatic to the brain. Recent evidence suggests tumors outside the brain are more electrically active than their normal tissues of origin (11). However, direct nerve-to-tumor cell synapses outside of the brain are still undefined. Exploiting two-photon and light-sheet imaging, in conjunction with electron microscopy and electrophysiology, will allow us to map innervation and the functional properties of synapses within the TME. Indeed, this is a strategy that has already proven successful in CNS malignancies.

Second, we require a deeper understanding of the role glial cells play in cancer, as peripheral nervous system glial cells, namely, Schwann cells, are essential for nerve outgrowth, regeneration, myelination, and survival. In cancer, these cells promote tumor dissemination along the nerve (PMID: 35881881; ref. 12), and Schwann cell lineage tumor growth (i.e., neurofibroma) in neurofibromatosis type I (NF1) can be enhanced via neural activity-driven secretion of soluble factors including collagen (13). Studying biomechanical and physiologic interactions between stromal, cancer, and neuronal components will require significant collaboration to define the mechanisms and biophysical constraints governing perineural invasion and cancer cell dissemination along nerves.

Third, we need a better understanding of how cross-talk between nerves and immune cells in the TME shapes local and systemic antitumor immune responses. Recent studies provide evidence that intratumor nerves can have opposing roles depending on the tumor site, which may in part be driven by the complex tissue specialization of the local immune compartment. Future studies should use fate-mapping strategies to tease out the interaction of intratumor nerves with circulating immune cells versus tissue-resident cells in the TME. Emerging data in immuno-oncology also show that there are discrete intratumor niches in patients that respond to immune-checkpoint therapy. These niches resemble tertiary lymphoid-like structures (TLS) and are enriched with poised effector CD8⁺ T cells important to sustain durable antitumor immunity. Preserving spatial information at the tissue level is critical. Therefore, future directions should utilize spatially resolved transcriptomics together with high-dimensional imaging (e.g., CODEX) to interrogate if the spatial organization of intratumor nerves is affected by immunotherapy, particularly in patients where TLS structures are found.

Fourth, we need a better understanding of how the presence and functional state of nerves within tumors dictate therapeutic efficacy. In triple-negative breast cancer, for example, chemical depletion of nerves or genetic deletion of nerve growth factor improves anthracycline-mediated control of metastasis (14). Genetic and chemical neuronal ablation techniques will be critical for establishing the functional role of intratumor nerves in response to chemotherapy, radiotherapy, hormonal, and immunotherapies.

A fifth major research area that requires attention revolves around understanding precisely how nerves grow into the tumor and how these nerves exert their effects on tumor biology. Current knowledge is mostly limited to the growth of preexisting nerves via paracrine signaling. However, other mechanisms, like adult neurogenesis and progenitor migration, are new avenues of research that can pave the way for harnessing neurogenic cues to shift the balance of tumor innervation toward a more hostile environment that will inhibit cancer progression or post-treatment recurrence (8). These tumor-associated nerves provide metabolic and trophic support to tumors, with recent work demonstrating that sensory nerves can supply the conditionally essential amino acid serine to pancreatic tumors in nutrient-poor environments (15).

Collaboration between cancer biologists, immunologists, and neuroscientists will pave the way to a better appreciation of the bidirectional dependencies between neural cells and cancers. We can expect multiple therapeutic opportunities from

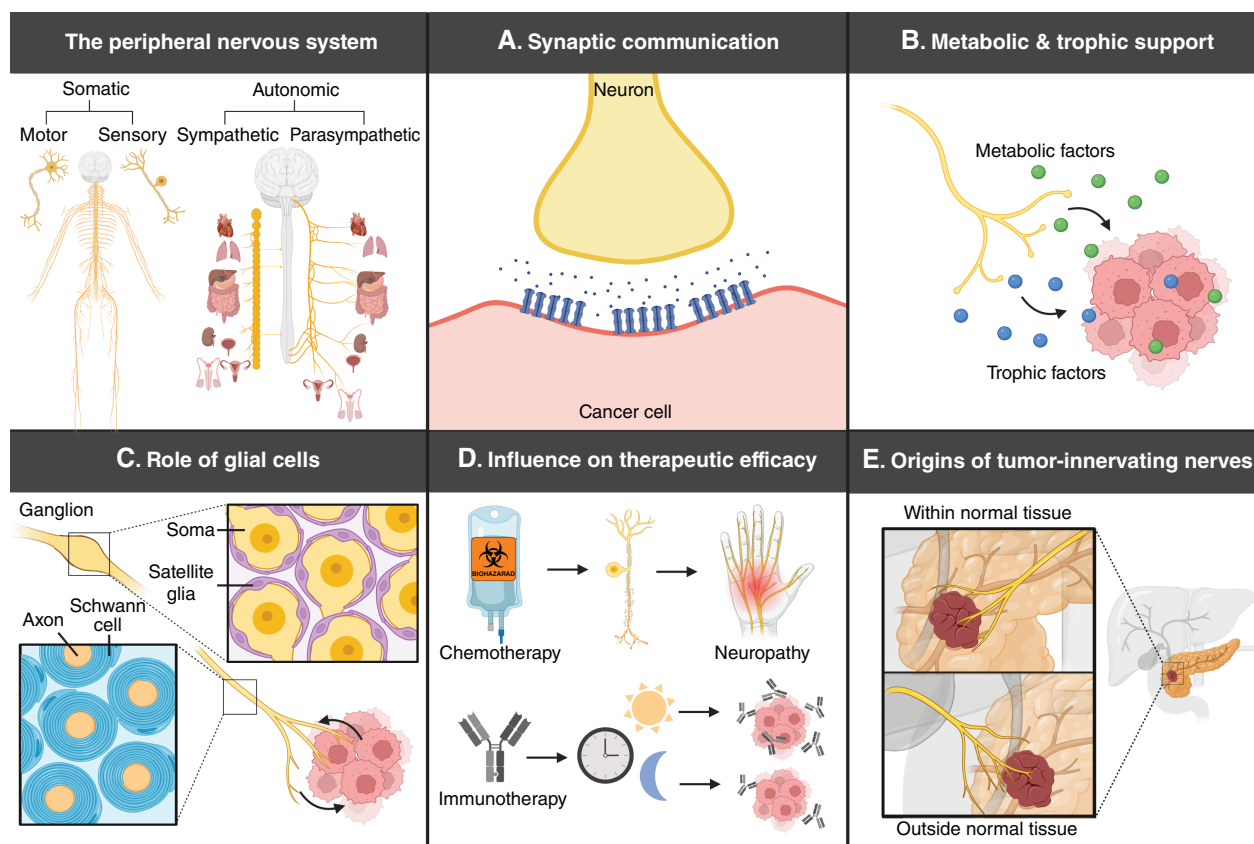


Figure 1. Key future directions in the neuroscience of cancers arising outside of the CNS. The peripheral nervous system (partitioned into somatic and autonomic subdivisions) is a major player in cancer pathophysiology. Emerging work highlights key research opportunities to define (A) synaptic and electrochemical interactions; (B) how nerves provide metabolic and trophic support to tumor cells; (C) how nerve-associated glial cells (e.g., Schwann cells or satellite glia) influence neuronal activity and tumor cell migration/perineural invasion; (D) how the presence and functional state of intratumor nerves influences therapeutic efficacy and neurotoxicity; and (E) where tumor-innervating nerves originate and how they become functionally and anatomically distinct from their normal tissue counterparts (Credit: Sarah Faber; BioRender).

these insights in the future. Indeed, the first neuroscience-instructed clinical trials have been started, and more are expected soon. However, for the successful development of a new pillar of cancer therapy, we need more fundamental scientific insights, tailored early trial concepts with biomarker-driven determination of target engagement, and the development of appropriate clinical readout measures. One barrier that has prevented more rapid progress in the field is that many of the tools needed to map and manipulate the PNS have not been optimized for use outside of the brain or spinal cord. Developing viruses with specific tropism for peripheral nerves and establishing electrophysiological techniques that maintain tissue integrity and neuronal innervation will be essential.

We further need to begin incorporating information on the nervous system and nerve-tumor interactions into our training materials for students interested in cancer biology. Interested neuroscientists need to additionally begin receiving training on the basic biology of cancer to put their work in context. Several cancer neuroscience-focused symposia and conferences are emerging, but these will need to be complemented by “hands-on” coursework where trainees can learn fundamental techniques that bridge each field. Finally, we need to incorporate patient experiences and feedback into our research objectives, especially

given the drastic effects cancer and its treatment can have on neurologic, affective, and cognitive functions.

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